Amendments to the claims

Claim 7 is amended to overcome the 35 U.S.C. §112, second paragraph rejection. No new matter has been added.

The 35 U.S.C. §112, second paragraph rejection

Claim 7 is rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Claim 7 is amended to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as helpfully suggested by the Examiner. Accordingly, Applicants respectfully request that the rejection of claim 7 under 35 U.S.C §112, second paragraph, be withdrawn.

The 35 U.S.C. §103(a) rejection

The rejection of claims 6 and 7 under 35 U.S.C. §103(a) is maintained, as being unpatentable over **Hallahan** *et al.*, U.S. Pat. No. 6,159,443, in view of the fact disclosed in the specification on pages 4, lines 15-20; 5, lines 1-5; and 10, lines 12-20, and **Mastrobattista** *et al.*, *Biochim. Biophys. Acta*, 1999, 1419: 353-363). This rejection is respectfully traversed.

The Examiner states that it would have been obvious to one skilled in the art to apply the teachings of **Mastrobattista** and the Specification to **Hallahan**, and substitute biomolecular carrier bearing antibodies to one cellular adhesion molecule (P-selectin) to biomolecular carrier bearing antibodies to another cellular adhesion molecule (ICAM-1), because the expression of either one of them would be enhanced in target tissue after irradiation, to obtain the claimed method of treating cancer by irradiating a target tissue or organ and administering the biomolecular carrier bearing antibodies specific to ICAM-1.

Applicant respectfully maintains that **Hallahan**, in view of Applicants' specification and **Mastrobattista**, do not provide the necessary teaching or suggestion that would provide a person having ordinary skill in the art to combine the elements of claims 6-7 with a reasonable expectation of success.

The specification describes the increase in expression of cell adhesion molecules, such as ICAM-1 and P-selectin, on the surface of endothelial cells in response to radiation, and that it would be ideal to deliver chemotherapeutic drugs specifically to the

irradiated tissues. **Hallahan** teaches the binding of a delivery vehicle comprising an active agent to a platelet, where it is the platelet that binds in turn to endothelial cells in the vasculature of the target tissue. The binding of the platelet serves to deliver the delivery vehicle/active agent in proximity to the target tissue, rather than direct binding of the delivery vehicle/active agent to the endothelial cell. **Mastrobattista** teaches liposomes bearing antibodies that bind to ICAM-1 expressed on the surface of cells, where such liposomes can be used as carriers to target delivery of anti-inflammatory drugs to sites of inflammation characterized by increased ICAM-1 expression. **Mastrobattista** does not teach liposomes carrying antbodies against P-selectin, nor the use of irradiation to increase the expression of cell adhesion molecules in the cells of a target tissue. **Mastrobattista** states that specific binding of the immunoliposome to cells in insufficient for effective drug delivery; the drug must also be delivered intracellularly; also, whether an immunoliposome is internalized or not depends on multiple factors, such as liposome size, the type of target cell, and the type of target receptor (see page 354, first full paragraph).

Considering the combined cited references, one skilled in the art would not have a reasonable expectation of success in combining the elements of claims 6-7. **Hallahan** does not provide motivation to bind an antibody delivery vehicle directly to a target receptor on a target cell, but rather teaches the binding of a delivery vehicle to a platelet, which in turn binds to the target cell. **Mastrobattista** teaches that a variety of factors influence the effective delivery of an active agent to a target cell, including the size of the liposome as a biodegradable particle, and the type of receptor. One skilled in the art would therefore not have been motivated to substitute the P-selectin receptor for the ICAM-1 receptor to arrive at the claimed method with a reasonable expectation of success. Therefore, the combination of the references lacks the requisite suggestion or teaching to motivate one skilled in the art to combine irradiation of a target tissue with administration of a biodegradable particle comprising an antibody or antibody fragment and a pharmaceutical, in order to deliver the pharmaceutical to the target tissue by binding of the particle via the antibody to P-selectin or ICAM-1 expressed on the surface of an endothelial cell. Accordingly, Applicants respectfully request that the rejection of claims 6-7 under 35 U.S.C. §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed October 22, 2002. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

DATE: June 9, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claim 7 as follows:

7. (twice amended) The method of claim 6, wherein said pathophysiological state is ~~selected from the group consisting of~~ cancer.